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| 10/770,885 | 02/02/2004 | Karl Y. Hostetler | UCSD1480-1 | 1066 |

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DLA PIPER LLP (US)
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

| EXAMINER | |
|---|---|
| MAEWALL, SNIGDHA | |
| ART UNIT | PAPER NUMBER |
| 1612 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/770,885 | HOSTETLER ET AL. | |
| | Examiner | Art Unit | |
| | Snigdha Maewall | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,7-12,23-25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7-12, 23-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Summary*

1. Receipt of Applicant's Arguments/Remarks, amended claims and **RCE** filed on 02/17/10 are acknowledged.

Claims 2-6, 13-22, 26 and 28-63 have been amended.

Accordingly, claims pending in this application are **1, 7-12, 23-25 and 27.**

**The rejections not reiterated herein have been withdrawn in light of applicant's submission of declaration.**

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Scope of Enablement**

3. Claims **1, 7-12, 23-25 and 27** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a pathological condition such as retinitis does not reasonably provide enablement for treatment of other ocular pathological conditions such as macular degeneration or ocular vascularization or

proliferation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method for treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex with ocular tissue..... as claimed in claims 1 and claim 25. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Maghami et al. (High Myopia and Pre-eclampsia: a blinding combination, accepted February 2006) , the reference teaches in pregnant woman with reduced visual acuity due to bilateral choroidal neovascularization to be untreatable and the treatment is still under investigation, see case report and discussion sections. Thus there is unpredictability in the treatment of ocular vascularization as noted by state of the art, in the absence of any scientific experimentation or data provided in instant specification, and without any defined subject population in instant claims, and due to unpredictability in the art, one of ordinary would undergo undue experimentation in order to practice the claimed

invention. The examiner also cites a Mayo clinic article which discloses that Stargardt's disease which is inherited form macular degeneration has no effective treatment, see under A. Similarly, another article provides unpredictability in treatment of macular degeneration such as age-related macular degeneration. There are two types of AMD, wet and dry and there is no cure for dry macular degeneration, see the whole article, 2 pages.

2. The breadth of the claims

The breadth of the instant claims 1 and 25 is very broad. The claims recite method of treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex of drug such as cidofovir, ganciclovir and arabinofuranosylguanosine in treating macular degeneration, ocular proliferative or vascular diseases and diseases of elevated intraocular pressure.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for treatment of ocular vascularization proliferation and macular degeneration and diseases of elevated pressures other than retinitis. The latter is corroborated by the working examples. See instant specification page 17.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used in treating macular degeneration and ocular vascularization as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success. It is to be noted that instant claims recite treatment of several pathological conditions; however no scientific experimental data is provided in instant specification regarding various conditions claimed with the use of the active agent complex. The claims also do not define how the complex is useful such as by slow release of the active complex and by utilizing specific amount and particle size. The claims do not define subject population, due to unpredictability shown in treatment of macular degeneration in pregnant women as discussed above, one of ordinary skill would undergo undue experimentation to practice the invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims **1, 7-12, 23-25 and 27** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 25 teaches ocular proliferative diseases which makes the claim indefinite because it is not clear whether applicant intends to claim ocular cancer diseases such as retinoblastoma (see USP 6,590,086) which teaches retinoblastoma as ocular proliferative disease. Since the specification does not provide any statement regarding such cancer therapy, examiner suggests reciting specific ocular proliferative diseases for which applicants have provide support in instant specification. Claims 23-24 recite the limitation of a method for slow release delivery of therapeutically effective drug, however the claims do not recite the drug is effective for which disease treatment or (pathological condition). Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims **1, 7-12, 23-25 and 27** are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (May 2000). (Investigative Ophthalmology &

Visual Science, May 2000, Vol. 41, No. 6, presented in IDS) in view of Ophthalmology 1983 Feb;90 (2); 121-5, abstract only and Machemer et al. (American Journal of Ophthalmology 112:159-165 august 1991).

Cheng et al. disclose that Cytomegalovirus (CMV) infection of the retina is the most common infection in acquired immune deficiency syndrome (AIDS) patients. (See page 1523, first paragraph).

Ganciclovir (GCV) was the first drug to be approved for CMV infection in AIDS patients. Ganciclovir is effective in treating CMV retinitis by intravenous administration, but the drug does not eliminate the virus from the retina, requiring long-term suppressive maintenance therapy. Systemic toxicity such as bone marrow suppression was also a problem. The sustained-release GCV implant is effective treatment for CMV retinitis and recurrent CMV retinitis, but complications from surgery such as endophthalmitis and retina detachment are sight threatening. Therefore, in an effort to overcome the disclosed threat, Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and **long-lasting for treatment of** CMV retinitis (page 1523, column 2, paragraph 2 and 3).

Cheng et al. further disclose the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinitis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. This type of self-assembling **liposomal prodrug**

provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases (page, 1531, last paragraph).

Because Cheng's references discloses the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinitis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and **other** intraocular viral infections in both immunocompromised and immunocompetent individuals., it would have been obvious to one of ordinary skill to have utilized such complex in treating other intraocular diseases such as ocular vascular diseases.

The reference does not relate treating ocular proliferative diseases by the complex.

The article by Machemer and the article of Ophthalmology teaches retinal detachment complicated with proliferation of membrane, see abstract. The reference teaches intraocular proliferation that is pigment clumps resulting from multiplication of pigmented cells in the vitreous matrix, see page 159 under grade A. The reference thus teaches association of retinal detachment with proliferative vitreoretinopathy.

Since Chang et al. teach that pathologic evaluation of eyes with retinitis showed retinal detachment, destruction of whole layers of retina with retinal cell necrosis accompanied by severe choroiditis and optic nerve inflammation; see page 1528 first

paragraph and figure 6 and Since the reference teaches treatment of retinitis with the claimed complex, one of ordinary in the art would have envisaged treating other pathological diseases and conditions such as ocular proliferation because Machemer discloses classification of proliferative vitreoretinopathy in four grades based on various symptoms and related retinal detachment with ocular proliferative disease. One of ordinary skill would thus have expected to utilize the complex taught by Chang et al. which teaches retinitis and teaches that retinitis can cause retinal detachment in treating intraocular proliferation because Machemer teaches retinal detachment with ocular proliferation and various grades of such based on various symptoms. Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to have treated retinal proliferation with the complex taught by Chang et al. because the article teaches association of retinal detachment with proliferation. It is to be noted that no there is no indication in independent claim1 regarding the complex being crystalline or amorphous or treatment by slow release of active or any particle size that is effective in the complex for the treatment. Absent evidence of unexpected results, the claimed invention is obvious within the meaning of 35 USC 103.

8. Claims **1, 7-12, 23-25 and 27** are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (May 2000). (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6, presented in IDS) in view of {(USP 5,516,522) OR (USP 5,098,443 A)} and vice versa.

Cheng et al. disclose that Cytomegalovirus (CMV) infection of the retina is the most common infection in acquired immune deficiency syndrome (AIDS) patients. (See page 1523, first paragraph).

Ganciclovir (GCV) was the first drug to be approved for CMV infection in AIDS patients. Ganciclovir is effective in treating CMV retinitis by intravenous administration, but the drug does not eliminate the virus from the retina, requiring long-term suppressive maintenance therapy. Systemic toxicity such as bone marrow suppression was also a problem. The sustained-release GCV implant is effective treatment for CMV retinitis and recurrent CMV retinitis, but complications from surgery such as endophthalmitis and retina detachment are sight threatening. Therefore, in an effort to overcome the disclosed threat, Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and **long-lasting for treatment of** CMV retinitis (see pages 1523, column 2 and paragraphs 2 and 3).

Cheng et al. further disclose the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinitis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. This type of self-assembling **liposomal prodrug** provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases (page, 1531, last paragraph).

The reference does not teach treatment of macular degeneration, ocular proliferation and vascular dieses.

'522 teaches slow release of drug for treatment of ocular diseases and teaches advantages of using slow-release drug delivery device in avoiding adverse effects on ocular structures. The reference teaches that such slow release feature will overcome some of the disadvantages caused due to surgeries of eye such as retinal detachment and proliferative disease caused due to retinal detachments or other eye disorders such as macular edema and vascularization. The reference teaches application of ganciclovir. See column 3, lines 10-40. The reference does not teach the complex of ganciclovir as claimed.

Since Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and **long-lasting for treatment of** CMV retinitis

(page 1523, column 2, paragraph 2 and 3) and since Chang teaches that complex provides longer and prolonged release of ganciclovir and overcomes the threats of endophthalmitis and retina detachment caused due to other treatment methods and '522 provides advantages due to slow release of ganciclovir in avoiding the ocular complications such as macular edema, retinal detachment and other vascular disease by utilizing slow release drug delivery mechanism, it would have been obvious to one of ordinary skill in the art at the time of instant invention to have utilized the slow release and long lasting treatment of ocular diseases and conditions by utilizing the complex of ganciclovir as taught by Chang et al. with a reasonable expectation of

success in treating ocular proliferative, macular degeneration and vascular diseases in a slow release manner without causing adverse ocular disorders or diseases.

Alternately, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have treated with the complex of ganciclovir because Chang teaches that complex provides longer and prolonged release of ganciclovir and overcomes the threats of endophthalmitis and retina detachment caused due to other treatment methods.

'443 teaches advantages of avoiding proliferative diseases, intraocular tumors, retinitis, reduction in scarred tissue in glaucoma surgery and other diseases and teaches utilization of ganciclovir in the controlled release process, see title , abstract and The reference thus emphasizes importance of slow release of ganciclovir in avoiding the complications of ocular diseases as occurred due to other treatment methodologies. The reference lacks the claimed complex of ganciclovir for ocular disorder therapy. Since Chang et al. disclose advantages of slow release and long lasting ocular treatment by using the claimed complex and since '443 emphasizes importance of slow release treatment therapies in avoiding ocular diseases , one of ordinary would have utilized the long lasting therapeutic profile by using Chang's complex with an expectation of success or alternately it would have been obvious too ne of ordinary to have utilized the instant slow release complex with ganciclovir in order to avoid the ocular adverse conditions or diseases because '443 teaches such advantages with controlled release drug delivery with ganciclovir and Chang teaches advantages in overcoming adverse effects due to utilizing complex of ganciclovir for

slow release. It is to be noted that no there is no indication in independent claim1 regarding the complex being crystalline or amorphous or treatment by slow release of active or any particle size that is effective in the complex for the treatment.

Absent evidence of unexpected results, the claimed invention is obvious within the meaning of 35 USC 103.

***Response to Arguments and Declaration***

9. Applicant's arguments with respect to claims **1, 7-12, 23-25 and 27** have been considered but are moot in view of the new ground(s) of rejection.

*The declaration filed on 02/17/10 is sufficient to overcome the rejection of record based Cheng et al. (Feb. 2002) (Investigative Ophthalmology & Visual Science, Feb. 2002, Vol. 43) because applicants have provided declaration under 37 CFR 1.131 that Chang et al. is applicant's own work and has filing date earlier than filing date of instant application and thus is not a prior art. As such the rejections based on the above reference have been withdrawn.*

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612